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ORIGINAL ARTICLE

The Effects of Diabetic Retinopathy and Panretinal Photocoagulation on Retrobulbar Blood Flow

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Abstract

Introduction: To evaluate effect of diabetic retinopathy and panretinal photocoagulation on retrobulbar blood flow together with systemic factors.

Methods: 62 Type 2 diabetic patients who either received or did net receive panretinal photocoagulation for variable stages of retinopathy and 15 control patients were enrolled in our study. BUN, creatinine and HbA1c levels for each subject have been determined. The ophthalmic artery and central retinal artery peak systolic velocity and end-diastolic velocity values were measured with color Doppler ultrasonography and resistivity indices were calculated.

Results: In diabetic group, lower blood flow velocities and higher resistivity indices were found in ophthalmic artery. There were no significant differences between the laser photocoagulation group and the preproliferative-proliferative retinopathy group as regards to blood flow velocities. BUN and creatinine levels increased with the stage of retinopathy. HbA1c levels were especially low in no retinopathy group with respect to others but there was no direct relation with the blood flow velocities.

Discussion and Conclusion: In diabetic patients retrobulbar blood flow velocities seems to decrease with the progression of retinopathy. Panretinal photocoagulation has no significant effect on these parameters. HbA1c levels seem to be related to stage of retinopathy.

Keywords: Color Doppler ultrasonography; diabetic retinopathy; retrobulbar blood flow.

Ocular blood flow is affected in diabetes in many ways, but the role of hemodynamics cannot be defined precisely. Color flow doppler ultrasonography (CD-USG), on the other hand, has attracted attention as a frequently used technique to examine retinal blood flow in recent years. In our study, we used CD-USG to detect flow changes in retrobulbar blood vessels in different stages of diabetic retinopathy. We also investigated the effects of pan-retinal photocoagulation (PRP), systemic factors and glycemic control on these parameters.

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Materials and Methods

Peak systolic velocity (PSV) and resistivity index (RI) were measured in the ophthalmic artery (OA) and central retinal artery (CRA) by CD-USG in 62 eyes of 62 Type 2 diabetic patients who were being followed up in the Ophthalmology Clinic of our hospital. The results were compared with the control group consisting of 15 subjects. For all procedures, patients were informed with the permission of the hospital management and their written consent was obtained.

In all cases, routine ophthalmological examinations including detailed fundus examination was performed, fasting blood glucose, blood urea nitrogen, creatinine and hemoglobin A1c (HbA1c) values were measured, and arterial blood pressure measurements were made. The right eyes of all cases, and if there was a stage difference between the two eyes, tthe eye with advanced involvement were evaluated.

Those who had a previous eye operation, history of glaucoma, ocular inflammatory disease or non-diabetic vascular disease were not included in the study. Group 1 consisted of 20 patients with Type 2 diabetes mellitus (DM) with normal posterior segment findings; Group 2 consisted of 15 patients with mild non-proliferative retinopathy with macular edema, hard and soft exudate, hemorrhage, and microaneurysms; Group 3 consisted of 16 cases in moderate and severe non-proliferative and proliferative stages with venous beading, intraretinal microvascular abnormalities and neovascularizations; and Group 4 consisted of 11 cases whose PRP was completed at least 3 months ago due to the proliferative stage. Laser treatment parameters were selected as 1400–2000 spots, 300–400 μm width, 250–700 mW energy level, and 0.1 s duration. Fifteen cases with no history of DM and normal anterior and posterior segment findings constituted the control group (Group 5).

Five patients in Group 1, 4 patients in Group 2, 4 patients in Group 3, 3 patients in Group 4, and 4 patients in Group 5 were under medication for hypertension. Those with premeasurement systolic blood pressure above 150 mmHg were not included in the study. CD-USG examination was performed by the same radiologist in all cases. Toshiba Power Vision 7000 SSA-380A CD-USG device was used in examinations. All analyzes were performed with a multifrequency (5-7.5-10 MHz) linear transducer. During the examination, the patients were placed in the supine position. All cases were informed about the study to be performed and their consents were obtained.

Statistical Package for Social Sciences for Windows 10.0 program was used for statistical analysis. In addition to descriptive statistical methods (Mean, Standard deviation), One-way analysis of variance and Tukey HSD Test were used to compare the normally distributed parameters of quantitative data, and Kruskal-Wallis test and Mann Whitney U test were used to compare our parameters that did not show normal distribution. Pearson's correlation coefficient was used to determine the relationships between parameters. Chi-squared test was used to compare qualitative data. The results were evaluated at the 95% confidence interval, with the significance level of $p<0.05$.

Results

Although the mean age of the control group was higher than the other groups, the age distributions did not differ significantly within the groups ($p>0.05$). There was a statistically significant difference between the groups according to the genders ($p<0.05$). The female ratio of Group 1 was found to be significantly higher than the other groups.

HbA1c levels differ significantly between study groups ($p<0.01$). The HbA1c level of Group 1 was found to be significantly lower than Group 2 ($p<0.01$), lower than Group 3 ($p<0.05$), and low compared to Group 4 ($p<0.01$).

PSV of CRA showed statistically significant differences between groups ($p<0.05$). CRA PSV of Group 5 was found to be significantly higher than Group 2 and Group 3 levels ($p<0.05$). While the CRA PSV level of Group 4 did not differ significantly compared to Group III ($p>0.01$), it also did not differ significantly with Group 1 and Group 5's levels ($p>0.05$). RI of CRA did not differ significantly between groups ($p>0.05$) (Table 1).

Table 1. Distribution of CRA PSV and RI levels by groups

CRA	Groups					p
	Group I (n=20)	Group II (n=15)	Group III (n=14)	Group IV (n=7)	Group V (n=15)	
PSV R	11.57±3.15	10.30±3.05	10.45±3.21	11.25±3.34	12.04±3.29	0.043*
RI R	0.67±0.06	0.64±0.08	0.66±0.09	0.68±0.08	0.64±0.05	0.610

*p<0.05 significant; PSV: Peak systolic velocity; RI: Resistivity index; OA: Ophthalmic artery; CRA: Central retinal artery.

OA PSV levels did not show a statistically significant difference between groups (p>0.05). However, OA RI levels showed significant differences between groups (p<0.01). OA RI of Group 1 was found to be significantly lower than Group 3 and Group 4 values (p<0.05). While the OA RI level of Group 2 was significantly higher than Group 5 (p<0.01), it did not differ significantly from Group 3 and Group 4 (p>0.05). While the OA RI levels of Group 3 were significantly different from Group 5 (p<0.01), there was no significant difference with Group 4 (p>0.05). OA RI value of Group 4 was significantly higher than Group 5 (p<0.01) (Table 2). It was observed that PSV and RI values of OA and CRA did not show a significant correlation with the HbA1c level (p>0.05). It was observed that the PSV and RI values of CRA did not show a significant correlation with the duration of diabetes (p>0.05). In OA, while PSV level did not show a significant correlation with diabetes duration (p>0.05), a positive and statistically significant correlation was found with RI (p<0.05).

Discussion

In previous studies, different methods were used to measure blood flow parameters in diabetic patients. Rimmer et al.[1] measured the foveal capillary circulation with the blue-light entoptic phenomenon; Grunwald et al.[2] used laser Doppler velocimetry to measure the velocity of erythrocytes in retinal vessels; and Konno et al.[3] measured blood flow in temporal retinal artery in diabetic patients using laser Doppler technique and monochromatic photography. In addition, two-point fluorophotometry,[4-6] photoangiography,[7] video fluorescein angiography[8] were used to evaluate retinal blood flow.

We used CD-USG, which is a relatively new technique, in our study. Today, CD-USG is accepted as a non-invasive, medication-free, reproducible, and rapid technique that provides the opportunity to evaluate the hemodynamic changes of retrobulbar vascular structures in real-time, under physiological conditions, and provides two-dimensional evaluation.[9] In measurements, it is superior to laser Doppler velocimetry and blue-light entoptic phenomenon, as it is not affected by factors such as visual acuity and media blur.

It is important to note that CD-USG measures blood flow velocities, not the amount of blood flow because it is impossible to accurately determine the diameter of orbital vessels in vivo with any technique. It has been reported in studies that RI is the hemodynamic parameter that is least affected by systemic and technical factors, and RI values are the most appropriate measurement for low-resistance vessels of the eye, which are minimally affected by errors in the interpretation of different studies.[10] In our study, we evaluated RI values together with PSV.

In the studies performed, no difference was observed between the right and left eyes in terms of Doppler values. In their study, Tamaki et al.[11] found no difference between the Doppler indices of the right and left eyes, while they found the mean ratios of the Vmax, Vmin, and RI values of the right and left eyes to be 1.03, 0.99 and 1.02, respectively. In our study, we evaluated one eye of all cases in order to avoid statistical errors. In general, the right eye was chosen, but in cases with a stage difference between both eyes (n=3), the eye with advanced stage was chosen.

In our study, especially in Group 1, there was a higher rate of females compared to other groups. Studies have found that gender does not affect CD-USG parameters.

Since one-third of the diabetic population is hypertensive, hypertensive patients were also included in the study. There was no significant difference between the groups in terms of blood pressure. Arterial blood pressure measurements of all patients were performed just before CD-USG examination. Those with systolic blood pressure above 150 mmHg and diastolic blood pressure above 90 mmHg were excluded from the study. Eight patients in Group 1, four patients in Group 2, six patients in Group 3, three patients in Group 4, and six patients in the control group were using different types of antihypertensives with a diagnosis of hypertension (Angiotensin-converting enzyme inhibitors, calcium channel blockers, and beta-blockers). Since these drugs are effective on vascular tone, they should be taken

Table 2. Distribution of CRA PSV and RI levels by groups

OA	Groups					p
	Group I (n=20)	Group II (n=15)	Group III (n=14)	Group IV (n=8)	Group V (n=15)	
PSV R	36.82±9.30	42.76±19.84	34.10±11.76	41.85±22.50	34.76±9.53	0.397
RI R	0.74±0.06	0.79±0.06	0.80±2.65	0.81±0.04	0.68±0.06	0.001**

**p<0.01 highly significant; PSV: Peak systolic velocity; RI: Resistivity index; OA: Ophthalmic artery; CRA: Central retinal artery.

into consideration when evaluating the results of our study.

The importance of glycemic control in the pathogenesis and progression of diabetic retinopathy is well known. Güven et al.[12] did not find a significant relationship between HbA1c and retinopathy stage in their examination of 73 eyes of 37 diabetic patients. There are findings in this direction in the literature.[13] In our study, we took the HbA1c values of the patients as a sign of glycemic control. In our evaluation, a significant difference was found between the groups in terms of HbA1c levels, and it was observed that HbA1c was significantly lower especially in the group without retinopathy than the other groups. It was observed that HbA1c values did not show a significant correlation with the PSV and RI values of OA and CRA.

Mac Kinnon et al.[14] found significantly higher RI in retinopathy groups at all stages compared to the control group in their study. This result was attributed to a statistically insignificant increase in PSV and a statistically insignificant decrease in end-diastolic velocity (EDV). Baştürk et al.[15] in their study with diabetic patients with microalbuminuria found that RI values increased significantly in the group with retinopathy, and they argued that RI value is an index that can be used in the follow-up of patients with diabetic retinopathy. Meng et al.[16] supported these findings in a recent meta-analysis they published.

According to our results, OA RI values were higher in the diabetic group than in the control group. There was a significant difference between the groups. OA RI values increase as the retinopathy stage progresses. There was no significant difference between Group 3 and Group 4. OA RI values also showed a significant positive correlation with the duration of diabetes. There was no significant difference between OA PSV values. A statistically significant difference was found between the CRA PSV values compared between the groups. Although CRA PSV values were significantly higher in the control group than in the diabetic group, a statistically insignificant high value was found in the PRP group compared to the non-applied group. Mendivil and Cuartero,[17] in their study, found a decrease in OA PSV values in the group that underwent PRP, compared to the group that did not.

Natori et al.[18] showed in their study that an increase in RI may be associated with an increase in peripheral vascular resistance, a decrease in systemic blood pressure, or a decrease in vessel diameter. Since there was no difference in systemic blood pressure between the groups in our study, the increase in OA RIs can be explained by increased peripheral vascular resistance or narrowing of the vessel diameter. Histopathological changes such as choroidal occlusion, basement membrane thickening, and capillary narrowing[19-22] seen in the choroid in diabetic patients explain the increase in peripheral vascular resistance. In addition, Garner et al.[23] found significant atheromatous stenosis in the OA in patients with diabetic retinopathy.

CRA PSV values were higher in the control group than in the diabetic group. According to Poiseulle's law, vessel diameter affects blood flow velocity. The decrease in CRA PSV values can be explained by increased peripheral vascular resistance or narrowing of the vessel lumen.

There was no difference in CRA PSV values in the PRP applied group compared to the non-applied group. Mendivil and Cuartero,[17] in their study, found a decrease in OA PSV values in patients who underwent PRP compared to the group with proliferative disease, that PRP was not applied. This result is explained in the article by increased retinal oxygenation. A decrease in ocular pulsation amplitudes was also detected after laser treatment,[24] which was also associated with the decrease in choroidal blood flow. In our study, however, no effect of photocoagulation on blood flow was observed.

There are few studies investigating the effect of anti-vascular endothelial growth factor agents, which have been widely used in the treatment of diabetic macular edema in recent years, on retrobulbar hemodynamics.[25-27] In the study conducted by Örnek et al.,[25] CD-USG showed a decrease in PSV and EDV values in CRA and nasal and temporal posterior ciliary arteries (TPCA) and a decrease in RI values in TPCA in the early post-injection period of ranibizumab.

In their study, Dimitrova et al.[28] found lower blood flow velocities in the posterior ciliary arteries in patients with baseline diabetic retinopathy compared to the control group, and they attributed these significant differences in the early stages to the upright posture given to the patients during CD-USG examination. In our study, the examinations were performed in the supine posture. This factor should also be taken into account when evaluating our results.

Conclusion

CD-USG is a non-invasive method that may be useful in identifying patients with a progressive course in diseases that may affect retrobulbar hemodynamics, such as diabetic retinopathy, and in which early treatment should be considered.

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